ALBERTA HERITAGE FOUNDATION
FOR MEDICAL RESEARCH

Technote

TN 40 OCTOBER 2003

SCLEROTHERAPY FOR VARICOSE VEINS OF THE LEGS

Request: This response addressed a request from the Alberta Health & Wellness, Claims Branch. The objective of this Technote is to inform on and to describe the current evidence to the following questions:

- Are there standards to determine when the treatment for varicose veins is considered medically necessary and when it is considered to be cosmetic?
- Is sclerotherapy effective as a medical treatment for varicose veins and, if so, is one approach more effective and for which group of patients (symptomatic, asymptomatic)?
- Are there new approaches or variations of sclerotherapy emerging?

BACKGROUND

The term "varicose veins" is used to describe dilated blood vessels under the skin of the legs, which have become visible, unsightly, abnormally enlarged or elongated, and/or knotted, tortuous, pouched, thickened or twisted [1-12]. For the purpose of this review the term varicose veins is used as an umbrella term to encompass all types of leg varicosities.

Leg varicosities can range from minor dilatations to large structures in the calf [1-12]. Very small varicose veins (<2mm in diameter) are referred to as venulectasia, telangiectasia, thread veins, spider veins, matted veins or dermal flares, and often occur alongside large varicose veins. Larger varicose veins include varicosities of reticular veins and "true" varicose veins representing varicosities of the saphenous veins and/or

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varicosities of their larger tributaries (see Figure 1). This category includes the largest diversity of varicose veins in terms of size (> 2mm in diameter) and depth below the surface.

Although numerous classifications have been proposed for varicose veins, there is still no universally recognized classification scheme for this condition [1-17]. There is also no consensus regarding definitions, optimal diagnostic procedures and treatment strategies for varicose veins.

Varicose veins

Varicose veins of the leg encompass the most frequent physical signs of chronic venous insufficiency (CVI) and is one of the most prevalent conditions in the general population [1, 2, 4-8, 10, 11, 15-21]. It is believed that they are caused either by primary abnormalities of the venous wall and/or valve leaflets or secondary changes due to previous venous thrombosis, both of which can lead to reflux, obstruction or both. Consequently varicose veins tend to be both chronic and recurrent. Most varicose veins are manifestations of primary venous insufficiency.

The prevalence of varicose veins is estimated to be between 2% and 40% [1, 2, 4-11, 13, 15-22]. Both prevalence and incidence increase with age in both genders but varicose veins appear to be more common in women than in men. There is evidence to suggest that 2.6% of women and 2.0% of men will develop varicose veins over a two-year period [13]. Risk factors for varicose veins include genetic predisposition (heredity), hormonal changes and pregnancy, obesity, lifestyle, venous thrombosis, leg injury, and prolonged standing [2-4, 15, 16, 18-21].

Varicose veins can be asymptomatic, produce aesthetic damage and/or discomfort or be responsible for functional and/or objective signs and symptoms of CVI [1-11, 13, 15-24]. The symptoms are not clearly defined and are not always related to the degree or size of the varicose veins. Also, the criteria used to differentiate between symptomatic and asymptomatic varicose veins are not yet clearly defined. Commonly reported symptoms include local discomfort (aching, pain, itchiness, and burning sensation), generalized lower leg symptoms (leg-tiredness, restless leg syndrome, heaviness, skin changes and swelling/edema) and cramps.

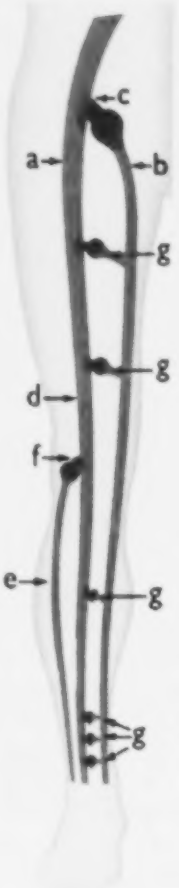

Figure 1
Source (20)

Key
a) femoral vein
b) long saphenous vein
c) saphenofemoral junction
d) popliteal vein
e) short saphenous vein
f) saphenopopliteal junction
g) perforating veins

Varicose veins of the leg, if untreated, may eventually lead to complications such as bleeding, thrombophlebitis, and leg ulcer (venous ulceration) [1, 4, 5, 9, 11, 13, 15, 18-21, 25]. However, varicose veins do not usually cause severe complications even if they are present over very long periods of time [5, 11, 12, 20, 21].

Treatment options

The actual cause of varicose veins of the legs remains unclear and there is no known cure [1, 4, 7, 11, 16-20, 26-28]. Treatment is palliative and aims to improve cosmetic appearance, relieve symptoms and prevent and/or manage potentially disabling complications. Asymptomatic varicose veins may be considered for treatment to improve appearance [2, 11, 16, 19, 20].

Treatment for telangiectasia and reticular varicosities is most commonly performed for cosmetic concerns and may not be considered medically necessary [2, 11, 12, 16, 17, 20, 21, 23, 27, 29-32]. Although most of the patients may be symptomatic as well [2, 16], these varicose veins are usually considered cosmetic problems that do not usually cause severe complications [5, 12, 20, 21, 27].

Patients with symptomatic varicose veins seek treatment to relieve symptoms and manage complications [11, 12, 20, 21, 23, 25, 29-32]. Treatment is considered medically necessary for symptomatic larger varicose veins (such as saphenous veins) associated with complications.

The variations in size, flow, depth and type of varicose veins preclude the possibility of a single effective treatment modality, particularly when viewed from a long-term perspective [1, 3, 4, 7, 8, 10, 16-19, 26]. Variables considered include the chronic and recurrent nature of the varicosities, the goal of the treatment, patient preference, complications associated with the treatment and cost-effectiveness. Criteria for evaluating success of treatment include clinical, aesthetic, haemodynamic and patient satisfaction factors. Recurrences may occur even after adequate treatment and lifelong control involves a series of treatments.

Currently, several treatment options are available depending upon the pathology and the severity of the condition [2-4, 8, 10, 11, 17, 25, 26, 33]. Conservative measures, such as compression therapy (e.g., bandages or stockings), are considered appropriate for small varicose veins with questionable symptoms or those with mild symptoms and no severe complications [2, 11-13, 19, 20, 25, 30, 31, 34]. When conservative measures fail and for more complicated cases, the main treatment options are sclerotherapy and/or surgery (procedures such as ligation, stripping, and stab avulsion). Many patients are treated using a combination of surgery, sclerotherapy and compression therapy. Other procedures such as radiofrequency ablation and laser therapy are currently being explored [2, 25, 35].

SCLEROTHERAPY

The focus of this TechNote is mainly on the safety and efficacy/effectiveness of the various sclerotherapy approaches for varicose veins (see Methodology, Appendix A). Sclerotherapy has been used worldwide (alone or in combination with surgery) to treat all types and sizes of varicose veins, primary and/or secondary in nature, with varying results.

Sclerotherapy as a treatment for varicose veins is a palliative and not an etiological treatment [4, 7, 9, 10, 17, 26]. It does not cure the varicose veins and is unable stop the formation of new varices. The general indications for sclerotherapy are to prevent complications related to varicose veins, to relieve symptoms and to improve the appearance of the leg.

Sclerotherapy is a procedure that has been advocated and used as an alternative to surgery or in combination with surgery for treating varicose veins since the 1960s [2-4, 6, 9, 10, 14, 17, 18, 27]. The guiding principle of successful sclerotherapy is to cause irreversible endothelial injury in the desired vein and eliminate all sources of superficial reflux without causing any adverse effects [3, 6, 7, 9, 10, 14, 16-18, 36-38].

Sclerotherapy generally requires multiple treatment sessions at intervals of 4 to 12 weeks, depending on the patient and the strength of the sclerosing solution [2, 17, 34, 39]. It may take up to 6 months for veins to completely go away. The procedure involves direct injection of a corrosive substance (sclerosing agent or sclerosant) into the varicose veins with a small needle. The sclerosant is designed to irritate or dehydrate, change the surface tension of or destroy the endothelial cells to produce a small thrombosis that eventually results in permanent fibrosis of the vein. After massaging the injection site to distribute the sclerosant more evenly, post-treatment compression therapy may be applied for few days or as long as 8 weeks [2, 3, 10, 14, 17, 19, 34, 40]. Patients require no hospitalization and remain mobile and active after sclerotherapy.

Patient evaluation and selection (based on a precise diagnosis of the varicose condition) are critical in determining the feasibility of using sclerotherapy [1, 2, 4-7, 9-11, 17, 18, 21]. Pre-treatment evaluation includes careful clinical history and physical examination and, when indicated, appropriate diagnostic tests (such as laboratory evaluation, duplex Doppler ultrasonography, plethysmography and other vascular testing).

Absolute contraindications for sclerotherapy include: known allergy to the sclerosing agent, severe systemic disease, recent deep venous thrombosis, local or general infection, inability to walk and severe arterial disease [4, 7, 9, 17]. Sclerotherapy should be performed with caution in pregnant or breast feeding women. It has been suggested that sclerotherapy should not be used when patients are fearful of needles, when sclerotherapy failed previously, and in patients with very fine telangiectatic vessels [14, 41].

Techniques

All sclerotherapy techniques used in clinical practice are derived from one of the three "historic" sclerotherapy techniques, known as French, Swiss, and Irish techniques [10, 14, 18, 36, 37, 42-44]. These methods differ in the overall treatment plan and in the use and duration of compression therapy following sclerotherapy.

A recent advance in traditional sclerotherapy is the new technique known as ultrasound-guided sclerotherapy (USGS) or echosclerotherapy, developed in the United States and Canada [10, 14, 28, 33, 38, 42, 45-47]. During USGS, the intra-venous position of the needle is controlled by both ultrasound and clinical observation. It purportedly increases efficacy and safety by providing visualization of the injection, diffusion of sclerosant and the venous spasm that follows injection, the immediate identification of a perivascular injection, unfavorable anatomical situations (such as incompetent saphenous junctions, trunks and perforating veins) and control of the results [8, 16, 18, 26, 43].

Despite the reduced likelihood of intra-arterial injection of the sclerosant, intra-arterial injections with USGS have been reported [10, 14, 28, 33, 38, 42, 45-47]. This has led to a further modification of the technique (referred to as endovascular sclerotherapy or transcatheter USGS) that involves using a catheter at the site of puncture (also called the "Canadian" method).

Foam sclerotherapy represents another advance [10, 15, 28, 38, 48-50]. Sclerosant solutions have been transformed into special foams for traditional sclerotherapy (without ultrasound guidance) of minor varicosities and for USGS to treat saphenous incompetence and recurrent varicose veins. Different methods have been developed to create stable sclerosing foam and each method has its own advantages and disadvantages. Recently developed sclerosing foams are believed to be stronger than sclerosant solutions and to act longer at the vein site.

The wide range of different practices in sclerotherapy suggests the lack of uniformity in performing this treatment [2, 4, 6, 7, 9, 10, 14, 17, 18, 36]. Techniques vary in terms of injection technique used (patient position and the type of agent, quantity, volume and concentration injected at any treatment site) [4, 6, 7, 9, 14, 17, 36]. Other variations include rate of injection, time between injections and duration of post-treatment compression therapy (which can be immediate or not, local or on the whole leg, and also vary in terms of type of material, and/or pressure/class).

To be qualified, the provider is required to have training in an appropriate specialty, knowledge of the anatomy and physiology of the venous system, a good understanding of the etiology of varicose veins, appropriate training in the evaluation and treatment of CVI and its manifestations, and knowledge of sclerotherapy mechanism of action [2, 4, 7, 9, 10, 14, 16, 17, 37-39]. Sclerotherapy is performed by dermatologists, family practitioners, internists and general, vascular and plastic surgeons [9, 17, 25]. Sclerotherapy for spider

veins is also carried out by specialist nurses under the supervision of experienced vascular surgeons [15]. Performance of USGS requires skills in both sclerotherapy and ultrasound and adds interventional radiologists to the list of people who now treat venous disorders [14, 16, 42].

The technique used, the type of sclerosant, experience of the provider, and other factors (including definition of recurrence and ultrasound factors such as ultrasonography experience and the resolution of the system used) have been identified as potential aspects that may influence the therapeutic outcome [2, 4, 6, 7, 9, 10, 14, 17, 18, 33, 36, 46].

Sclerosing agents

Sclerosants can be classified into detergents, chemical irritants, and osmotic agents (see Appendix B, Table 1). The mechanisms by which these agents produce endothelial injury vary. They also vary in their sclerosing power, concentration, the pain provoked on injection and the incidence of other adverse effects. Although a variety of sclerosants are currently available, the ideal agent (which would achieve endothelial damage, sclerosis of the vein and clinical obliteration without any adverse effects) is yet to be developed [2, 6, 9, 10, 17, 18, 46].

There is no universal consensus regarding the use of a specific sclerosant, its concentration or dose and for which specific type of varicose veins. The choice of sclerosant appears to be based on: its approval by regulatory bodies such as the Food and Drug Administration (FDA) in the United States and Health Canada; its minimum concentration and complication profile; patient's allergy profile, pain tolerance and previous treatment response; the type, size and site of the veins to be injected; and the provider's personal knowledge and experience [2, 3, 8, 10, 14, 17, 18, 51]. The concentration and injected volume of the sclerosing agent also depends on the interval between injections; and whether it is the first injection or a re-injection [3, 6, 7, 9, 10, 14, 16-18, 36]. The duration of direct contact the agent has with the walls of the veins appears to be even more important than the volume or rate of injection [14, 28, 36, 37, 47, 52].

Side effects and complications

Sclerotherapy for varicose veins of the legs has been associated with various adverse effects [2-4, 6, 9-11, 14, 17, 18, 35, 38, 44, 52-54] including:

- pain with injection, itching, cramps;
- slight or severe cutaneous pigmentation or hyperpigmentation (rates reported between 10% and 80%; temporary pigmentation (6-24 months) reported in about 10-30% of cases and permanent pigmentation in 5-7% of patients [52,53];
- localized urticaria;
- secondary telangiectasia or matting (rates vary between 5% and 75%);
- chemically induced phlebitis or periphlebitis;

- cutaneous necrosis or ulceration resulting in scar formation (in experienced hands rates of <1%); and
- blurry and temporary loss of vision (sodium tetradecyl sulfate and chromated glycerine).

Major complications are very rare, but dramatic, and include accidental intra-arterial injection, deep venous thrombosis, superficial thrombophlebitis, pulmonary embolism, and systemic allergic reaction (anaphylactic shock) [2, 3, 6, 9-11, 14, 17, 18, 35, 36, 38, 54].

The occurrence of simple complications such as matting (neurovascularization) and pigmentation is less acceptable when sclerotherapy is performed for cosmetic purposes rather than for functional venous disorders. Therefore, patients should be informed about the possible side effects [4, 7, 9, 11, 55].

Regulatory approval and coverage

The most commonly used sclerosing agents are sodium tetradecyl sulfate (STS), hypertonic saline, hypertonic saline dextrose, polidocanol (POL), and chromated glycerine [2, 3, 10, 14, 17, 18, 44]. STS, a detergent, is FDA approved and licenced by Health Canada (see Appendix B, Table 1). Polidocanol, also a detergent, is currently undergoing FDA review and requires special approval from Health Canada. Hypertonic saline dextrose, an osmotic agent, is not approved as a sclerosant by the FDA. However, *Sclerodex®* is widely used in Canada, and is licenced by Health Canada for local injection in sclerotherapy, but. Chromated glycerine (*Chromex®)* is a chemical irritant widely used in Europe but is not available in North America.

In Alberta, the physician component for the injection(s) of sclerosing agents into symptomatic veins is an insured service when deemed medically necessary [56]. If the treatment is for cosmetic reasons it is not covered by the Alberta Health Care Insurance Plan.

In the United States, health insurance coverage for sclerotherapy (with or without ultrasound guidance) as a treatment for varicose veins varies (see Appendix C, Table 2). Insurance coverage is considered both on the basis of the agent and the technique. In general, sclerotherapy is considered medically necessary and is covered when performed for symptomatic varicose veins that have failed previous conservative treatment (such as compression therapy) of 1.5 to 6 months duration. Insurance plans may not cover treatment of spider veins if the treatment is performed solely for cosmetic reasons.

Ultrasound or duplex-guided sclerotherapy techniques are considered investigational and reimbursement is not available when they are performed solely to guide the needle or introduce the sclerosant into the varicose veins [29-32, 57]. A coverage policy by the Health Administration Center of the Department of Veterans Affair [58] approved USGS

for use on the lesser and greater saphenous vein system when the medical record documents a justified need for ultrasound as an adjunct to sclerotherapy.

Available Evidence on Efficacy/Effectiveness and Safety

The literature search revealed no RCTs that compared sclerotherapy (with or without ultrasound guidance) with other non-surgical options (such compression therapy) or watchful waiting.

The available evidence will be presented according to the treatment approach and the level of evidence (randomized controlled trial or systematic review). Details of the reviewed randomized controlled trials (RCTs) are summarized in Appendix D, Table 3.

Randomized controlled trials

Two **RCTs** compared the safety and efficacy of **different liquid sclerosing agents** [59, 60]. Goldman [59] evaluated the safety and efficacy of **POL versus STS** in 129 patients with **varicose, reticular and/or telangiectatic leg veins without incompetence at the saphenofemoral or saphenopopliteal junctions**. All patients had an average of 70% improvement and 72% of patients in all vein categories treated were satisfied with either solution. There was no significant difference in adverse effects between groups. There was a significant decrease in ulcerations and swelling in the POL-treated group. POL had a similar effect on vein obliteration, but a higher improvement score and higher overall patient satisfaction than STS. Based on these results, the investigator concluded that both solutions were safe and effective sclerosing agents for varicose and telangiectatic leg veins.

McCoy et al. [60] compared the relative efficacy of **hypertonic saline (HS) and POL** for **primary idiopathic leg telangiectasia and reticular feeding veins (with no evidence of major saphenous or perforator incompetence)**, using each patient as her own control. HS was equally effective as POL but POL caused more staining and matting. Although patients found HS more painful at injection, patient satisfaction at follow-up was higher with HS compared to POL. The investigators concluded that both agents have equal efficacy in sclerosing reticular feeding veins and telangiectasia. However, POL caused more adverse effects, which might have been related to the concentration used. No post-treatment graduated compression was used in this study.

An **RCT** by Lupton et al. [61] compared the efficacy of treating **leg telangiectasia** with **STS sclerotherapy versus long-pulsed 1064 nm Nd:YAG laser irradiation**. The results suggested that patients with leg telangiectases responded better to sclerotherapy and had fewer treatment sessions than those patients treated with laser irradiation. Earlier vessel clearing was observed and higher improvement scores for sclerotherapy were noted at each follow-up visit. The incidence of adverse effects was minimal and equivocal in both treatment groups. The investigators concluded that "sclerotherapy

continues to offer superior clinical effect in the majority of cases" and leg vein treatment with laser irradiation "appears to be most beneficial in patients with telangiectatic matting, needle phobia, or sclerosant allergy".

The RCT by De Roos et al. [62] compared the recurrence rates and incidence of complications after **compression sclerotherapy and ambulatory phlebectomy** (AP) for **lateral accessory varicose (LAV) vein** (second largest superficial vein described as "a tortuous and dilated vein typically on the anterolateral side of the thigh"). Investigators reported significantly lower 1- and 2-year follow-up recurrence rates after AP than those observed after sclerotherapy. Statistically significant differences in complications (blisters, telangiectatic matting, scar formation and bruising from bandaging) occurred more frequently in the AP group than the compression sclerotherapy therapy group.

A recent **multicentre RCT** by Belcaro et al. [63] reported results from the Venous Disease International Control Trial (VEDICO) based on 749 patients randomly treated by six different approaches: **standard sclerotherapy, standard sclerotherapy with high dose STS, surgical ligation, stab avulsion (SA), foam sclerotherapy and combined surgery (ligation or SA) and high dose sclerotherapy**. Patients with uncomplicated primary varicose veins (associated with **incompetence of the long saphenous vein**) were evaluated pre- and post-treatment at 5 and 10 years.

Low dose standard sclerotherapy was less effective than high dose sclerotherapy and foam sclerotherapy using measures of occurrence of new varicose veins at 5 and 10 years. At 10 years the occurrence of new veins was 56% for standard sclerotherapy, 51% for foam sclerotherapy, 49% for high dose sclerotherapy, 41% for SA, 38% for ligation, and 27% for combined surgery and sclerotherapy.

This was the first long-term RCT on foam sclerotherapy. Even though this trial indicates that it is efficacious when compared to standard sclerotherapy, it still needs some refinements and should only be provided by specialists.

The authors noted that even at centres of excellence there were no definite standards for the treatment of varicose veins. Evaluations were not yet standardized and quality of life assessments should be included in future research. Based on ambulatory venous pressure measure and refilling times, the authors concluded that all treatments may be similarly effective when appropriately performed.

One **RCT** by Belcaro et al. [64] evaluated the efficacy and costs of **endovascular sclerotherapy (ES) (with high resolution ultrasound) compared with surgery alone or combined surgery and compression sclerotherapy** in patients with **varicose veins and simple superficial venous incompetence**. Although all approaches were reported to be effective in controlling the progression of venous incompetence, surgery appeared to be the most effective method on a long-term basis. This study suggested that combined surgery and compression sclerotherapy may be more effective than surgery alone,

particularly for distal veins. However, both surgery and surgery combined with compression sclerotherapy were more expensive than ES (which was also followed by compression of residual veins for three months).

Based on their results, even though there was an 18.8% failure rate in controlling saphenofemoral junction incompetence and a 43.8% failure in obliteration of distal saphenous reflux following ES (16.1% combined surgery and sclerotherapy; 36% surgery alone), the investigators concluded that ES was an effective, cheaper treatment option.

Systematic reviews

One Cochrane **systematic review** by Tisi and Beverly [13] was found that aimed to determine whether sclerotherapy is effective in terms of symptomatic improvement, recurrence and cosmetic appearance, and has an acceptable complication rate. This review intended to include RCTs of **injection sclerotherapy versus graduated compression stockings or 'observation', or comparisons of different sclerosants, doses and post-compression bandaging techniques** on patients (> 15 years of age) with symptomatic and/or cosmetic varicose veins. Patients with venous ulcers were excluded.

The reviewers found that there was very limited evidence on which to assess the relative merits of sclerotherapy as a treatment for varicose veins. The methodological quality of many of the ten included RCTs was considered questionable. The main problems with the trials appeared to be in the randomisation process and in blinding of the patient and/or observer to the treatment. Most RCTs (9/10) dated back to the 1980s.

Comparisons of STS to alternative sclerosants indicted that there was no significant benefit from using alternative sclerosants to STS. The addition of local anaesthetic to the sclerosant reduced the pain from injection. Comparison of two pressure dressings showed that there was no difference in their effect on erythema or the success of the sclerotherapy. The degree and duration of compression (elastic) had no significant effect on recurrence rates, cosmetic appearance or symptom improvement.

The reviewers noted that the place of sclerotherapy in modern clinical practice is limited to treatment of recurrent varicose veins following surgery and thread veins. There was no objective evidence to support or not support the continued use of sclerotherapy. However, the reviewers recommended consideration of their results in conjunction with findings from an ongoing Cochrane review (by Michaels and Kendall) that will assess RCTs comparing surgery to sclerotherapy and help determine the overall place for sclerotherapy as a treatment for varicose veins.

Upcoming studies

The National Coordinating Centre for Health Technology Assessment in the United Kingdom is currently undertaking a review that will assess the cost-effectiveness of the commonly used treatments for varicose veins by way of a Markov decision model [65]. The model will allow an assessment of the incremental cost-effectiveness of each treatment modality (conservative treatment, sclerotherapy and surgery) in sub-groups of patients based upon their symptomatic, investigative and demographic features. This review is expected to be published in 2004.

CONSENSUS DOCUMENTS AND GUIDELINES

Three consensus reports [1, 4, 7] and one guideline document [9] were located and their recommendations on sclerotherapy are summarized in Table 4.

Table 4: Summary of recommendation from consensus reports and guidelines

Condition	L'ANAES [1]	VEINES [4]	International Consensus [7]	American Academy of Dermatology [9]
All stages of primary varicose veins	Surgery to relieve symptoms or prevent complications			
Telangiectasia, reticular varicose veins, symptomatic without reflux	No surgery	Sclerotherapy to relieve pain		
Telangiectasia, reticular varicose veins with superficial venous reflux	No surgery	Sclerotherapy (improvement in cosmetic appearance)		
Venulectasia, Telangiectasia and small varicose veins (reticular veins)	No surgery	No surgery	Sclerotherapy	Sclerotherapy
Non-saphenous varicose vein including residual and recurrent varicosities after surgery, local varicose and varicose tributaries to saphenous trunk without saphenous insufficiency		Sclerotherapy	Sclerotherapy is adequate; choice between surgery or sclerotherapy based on physician's experience and vein characteristics	

Table 4: Summary of recommendation from consensus reports and guidelines (cont'd)

Condition	L'ANAES [1]	VEINES [4]	International Consensus [7]	American Academy of Dermatology [9]
Large tributaries feeding varicose veins but without evidence of reflux in the large veins		Surgery		Sclerotherapy (branch of truncal varicose vein or mid and posterior thigh perforating vein) Duplex USGS (perforating veins)
Saphenous veins with reflux	Surgery	Surgery		
Long saphenous varicose veins		Surgery (treatment of choice for saphenous varicose veins)	No agreement on role of sclerotherapy	Sclerotherapy (after appropriately treating all points of reflux)
Short saphenous veins		No evidence if surgery or sclerotherapy is best option	Either surgery or sclerotherapy	Sclerotherapy (after appropriately treating all points of reflux)

L'Agence Nationale d'Accreditation et d'Evaluation en Sante (l'ANAES) conducted a systematic review of the literature on the indications of surgery for varicose veins of the lower limbs [1]. Given the lack of good scientific evidence on the various treatments for primary varicose veins, the working group made recommendations based on professional agreement. They concluded that although surgery and sclerotherapy are frequently associated, the benefit of this association has yet to be demonstrated. Surgery and sclerotherapy generally do not address the same patients, and a better definition of the populations who should be treated with surgery and/or sclerotherapy is needed.

The Venous Insufficiency Epidemiologic and Economic Studies (VEINES) task force conducted a systematic review of the evidence published between 1966 and 1996 on chronic venous disease of the leg (CVDL) [4] and based their recommendations on these findings. CVDL was defined as an umbrella term that encompassed the various clinical presentations of chronic venous insufficiency, namely venous symptoms, edema, telangiectasia, reticular veins, varicose veins, skin changes and venous ulcers.

Given the lack of agreement on the techniques, clinical indications and results of sclerotherapy for varicose veins of the legs, international consensus conferences were organized during the mid 1990s [7, 55]. The conferences took into consideration the

scientific literature available, the personal experiences of the participating experts and the results from an international questionnaire concerning the practice of sclerotherapy. The experts noted the lack of RCTs and the fact that there was no universally recognized classification before 1994, making inter-study comparisons difficult [7]. Given the lack of relevant literature, recommendations could not be made regarding the most appropriate technique of performing sclerotherapy. This would depend on the expertise and the preference of the operator.

Recently, the American Academy of Dermatology [9] developed guidelines for sclerotherapy of varicose and telangiectatic leg veins using sclerosing solutions. They suggested that Duplex USGS may be used for the treatment of perforating veins because of the likelihood of perforating arteries and nerves running adjacent to the perforating veins.

Expert Opinion

The literature search identified three questionnaire-based studies regarding the practice of scleortherapy [44, 66, 67]. Their findings are summarized below as an indicator of expert opinion.

Two papers [44, 66] reported results obtained from surveys of the members of the Vascular Surgical Society of Great Britain and Ireland regarding the practice of sclerotherapy. Galland et al. [44] showed that as many as 70% of respondents used sclerotherapy as their treatment of choice for primary varicose veins when there was no proximal incompetence, and that 77% used it after surgery for residual varicose veins. This study also indicated that surgeons' interest for using sclerotherapy to treat varicose veins was decreasing and more patients were being referred for surgery.

Lees et al. [66] reported that although 60% of respondents used sclerotherapy for varicose veins, only 1.1% were providing it as an alternative to surgery in patients with incompetent long and for short saphenous veins. Surgery was the preferred option for these indications. The main indications for sclerotherapy were for missed/residual varicose veins following surgery (60%), isolated small varicose veins (73%) and thread veins (50%).

Eleven phlebological societies participated in an international practice survey on sclerotherapy for varicose veins [67]. The results showed that sclerotherapy was used less in countries where the respondents were surgeons (such as Scandinavia and United Kingdom). In Canada, sclerotherapy was used by many specialists in angiology (92%). The survey identified a wide range of practices in sclerotherapy and the technique used seemed to depend on the country rather than on the basis of results obtained from clinical trials.

The results indicated surgery as the preferred treatment for incompetent greater saphenous veins[67]. However, about 30% of physicians in Canada, France, Japan and the United States provided sclerotherapy for this indication. Replies from surgically dominated countries (such as United Kingdom, Scandinavia and Australia) mainly recommended surgery for lesser saphenous veins. When treating perforator veins, both sclerotherapy and surgery were used. Sclerotherapy was identified as the treatment of choice for reticular veins by most respondents. Almost all doctors preferred sclerotherapy for the treatment of telangiectatic veins.

DISCUSSION

Sclerotherapy is a dynamic procedure that has evolved during the last four decades. It has been proposed as a non-surgical treatment option and has been frequently used (alone or in combination with surgery) for all types of varicose veins. However, the exact role of sclerotherapy in the management of varicose veins and its association with surgery remains to be addressed.

The reviewed evidence does not adequately address the questions: which sclerosant is superior and which technique with or without ultrasound guidance is most efficacious. The results from the two RCTs [59, 60] that attempted to answer the question which sclerosant is more effective were not comparable. Although clinically their study populations seemed similar, their investigators took different approaches. Each study had different treatment protocols, used different sclerosants with varying concentrations and evaluated treatment outcomes using different measures. These studies reported results from very short follow-up times (8 to 16 weeks) [60].

The systematic review provided a general conclusion based on limited evidence from relatively old studies that there is neither support or no support for sclerotherapy, but its role may be more clearly defined by an upcoming Cochrane review. Among the RCTs reviewed in our study, the one by Lupton et al [61] compared sclerotherapy with laser irradiation for treating patients with leg tangiectasia and indicated that clinical improvement scores were better for sclerotherapy.

The reviewed literature suggests that there are still some high priority areas for research in this field [4, 5, 7, 13, 14, 25, 26, 44, 67]. There is a wide variety of techniques and criteria for an objective evaluation of their efficacy are still debated . There is a need for uniformity and objectivity for diagnosis, patient selection criteria, definition of treatment failure, appropriate outcome measurement and definition of recurrence.

In recent years, new methods such as ES and foam sclerotherapy (using ultrasound guidance) have been developed and proposed to improve the safety and efficacy of sclerotherapy for various types of varicose veins. Evidence about these new techniques for treating patients with incompetence of the long saphenous vein is limited [63, 64]. Only one study [64] used ES with high resolution ultrasound to treat patients with pure

superficial venous incompetence; however there was no comparison with standard sclerotherapy, only with combined surgery and standard sclerotherapy. The new methods may well offer some advantages for certain patients, but they need further stringent evaluation.

CONCLUSIONS

Treatment of varicose veins of the legs is a field that has many conflicting claims. Although varicose veins are a common finding in the general population, there is still no consensus regarding their definition, or the optimal diagnostic procedures and treatment strategies based on the type of varicosity. Symptom relief is one of the main reasons for which treatment of varicose veins is considered. However, the specific symptoms and criteria that differentiate between symptomatic and asymptomatic varicose veins are not clearly defined.

Consensus regarding generally accepted criteria to determine when treatment for varicose veins of the legs is medically required and when it is to be considered cosmetic, have yet to be established. There appears to be general agreement that treatment for telangiectasia and reticular varicosities is considered to be cosmetic as these varicosities usually do not cause complications.

The role of sclerotherapy, particularly in relation to other types of treatment for varicose veins, has yet to be clearly defined. The reviewed literature from 1998 onwards, although limited, reflects the following if used by an experienced provider:

- Sclerotherapy appears to be the treatment of choice for reticular varicosities, telangiectasia and other small, unsightly blood vessels.
- The place of sclerotherapy as the first treatment for larger varicose veins (saphenous or non-saphenous) remains controversial.
- Sclerotherapy following surgery may achieve good results in varicose veins which have not fully disappeared or recur.
- Currently, the appropriate techniques and sclerosing agents to be used for various types of varicose veins are still debated.
- POL, STS and HS are potentially safe and effective in the short-term. There is no standard protocol for their use.
- Endosclerotherapy and foam sclerotherapy (with ultrasound guidance) appear to be efficacious.

Sclerotherapy requires multiple injections and is associated with many complications including the possibility of systemic allergic reactions to the injected sclerosant, post-treatment ulceration, scarring, telangiectatic matting.

In North America, health insurance coverage for sclerotherapy as a treatment for varicose veins varies. If the treatment is done for cosmetic reasons only, it is generally not covered.

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Technotes are brief reports, prepared on an urgent basis, which draw on limited reviews and analysis of relevant literature and on expert opinion and regulatory status where appropriate. They are not subject to an external review process.

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APPENDIX A: METHODOLOGY

LITERATURE SEARCH

A computer search for published articles (1998-present) on the safety and efficacy/effectiveness of using sclerotherapy in patients suffering from varicose veins of the legs was conducted. The search was limited to human studies, English, reviews and RCTs.

Of the databases and information sources searched, the following identified relevant literature and related materials:

- PubMed (searched April 2, 2003);
- EMBASE (Ovid; 1996 to 2003 Week 13);
- The Cochrane Library (Issue 1, 2003);
- MEDLINE and PREMEDLINE (Ovid; 1966 to March Week 3, 2003);
- CRD databases (HTA, DARE, NHS EED; Searched April 2, 2003);
- Ovid HealthSTAR (1987-March 2003);
- ECRI (Searched April 2, 2003)
- Web of Science (Social Sciences Citation Index and Science Citation Index Expanded; Searched April 2, 2003);
- NEOS (NEOS library consortium catalogue)

The keywords (used alone or in combination) included: sclerotherapy, leg or legs, leg veins, varicose veins, varicose-veins, varicose veins/therapy, varicose veins/surgery, varicosis, and leg varicosis.

In addition, the following Internet sites were checked (April 2003):

- Alberta Medical Association (sclerotherapy)
- Blue Cross Blue Shield, Technology Evaluation Centre
- Cabot (Canadian Health Research Index) (varicose veins, sclerotherapy)
- ClinicalTrials.gov (varicose veins, sclerotherapy)
- CMA INFOBASE: Clinical Practice Guidelines (sclerotherapy or varicose veins)
- Institute for Clinical Systems Improvement (ICSI)
- NLM Gateway (varicose veins AND sclerotherapy)
- National Guideline Clearinghouse (sclerotherapy or varicose veins)
- National Institute for Clinical Excellence (NICE) (varicose)
- National Research Register (Issue 1, 2003) (sclerotherapy and varicose veins)
- STEER

- University Health System Consortium (UHC)
- U.S. Food & Drug Administration

A broad Internet search was also conducted using the meta-search engine (Copernic Agent 6.0 (sclerotherapy, varicose veins). The reference lists of all articles were examined for studies/papers that were missed by the electronic searches.

The review of the literature was supplemented with information from:

- Health Canada, Therapeutic Products Directorate for information on regulatory status of various sclerosing agents in Canada; and
- Dr. Jonathan Michaels, Clinical Director, Sheffield Vascular Institute in the United Kingdom, member of the Cochrane Peripheral Vascular Diseases Review Group for information on the current stage of the Cochrane review of RCTs comparing surgery versus sclerotherapy for varicose veins.

Screening and Reviewing the Literature

The studies identified by the search strategy were retrieved, reviewed and assessed to determine the relevance of each study; their inclusion/exclusion was decided by one reviewer. Suitability for inclusion in the review was determined on the basis of a list of inclusion and exclusion criteria developed for this study.

Included were:

- published reports of RCTs;
- systematic reviews and critical appraisals;
- guidelines, position papers, consensus statements or minimum standards for the use of sclerotherapy to treat varicose veins;
- guidelines, position papers, consensus statements on definition diagnosis or treatment of varicose veins;
- overview articles, commentaries and discussion papers presenting background information on the topic.

Non-randomized controlled trials, cohort studies, case series, case reports, editorials, letters and technical reports were not included.

Although mostly articles published in English and after 1998 were selected, some papers (presenting relevant information on the topic) published in French and/or before 1998 were retrieved, translated by one reviewer and quoted when appropriate.

Details of the RCTs included for review and their results are summarized in tabular format (see Table 3, Appendix D).

APPENDIX B: SCLEROSING AGENTS

Table 1: Sclerosing agents [2, 3, 14, 17, 18, 36, 51, 59, 68]

Agent (brand names)	Description and Usage	Complication profile	Regulatory status
Hypertonic saline (HS) Brand names: None	- hyperosmotic agent; caustic sclerotic action; readily available; rapid action - commercially available in 20% or 23.4% concentrations - less effective for larger thicker-walled varicose veins; mostly used for telangiectatic veins	Pain (stinging and cramping) High risk of skin necrosis Highly ulcerogenic Hyperpigmentation Low allergenic risk	FDA approved as abortifacient; Not FDA approved as sclerosant; under FDA review
Sodium salycilate Brand names: Saliject	- hyperosmotic agent; - produced as a 57% solution - needs to be diluted to 6% and 30% concentrations for general use	Very painful upon injection	Saliject is licensed by Health Canada for local injection in sclerotherapy
Hypertonic saline dextrose (HSD) Brand names: Sclerodex	- mild hyperosmotic agent (similar to HS); - characterized by high viscosity; remains in treated veins - available in one concentration only - less effective for larger thicker-walled varicose veins	Pain and muscle cramps (less than with HS) Low allergenicity Low risk of skin necrosis	Not FDA approved as sclerosant; Sclerodex is licensed by Health Canada for local injection in sclerotherapy
Sodium tetradecyl sulfate (STS) Brand names: Sotradecol, STD, Tromboject, Trombovar	- detergent (emulsifier); expensive; strong sclerosing effect; rapid dissolution of endothelium; effective at low concentrations - commercially available in 0.5% to 3% concentrations; - higher concentrations used for large veins (1.5%-3%) - can be diluted for use in telangiectatic and reticular veins (0.1% to 1% commonly used)	Pigmentation Necrosis of skin (with extravasation of concentrations >0.25% concentration) Painless with intravascular injection and painful with extravascular injection Rare anaphylaxis	FDA approved for treating vascular ectasias of the lower extremity; never formally investigated as a sclerosant agent for varicose and telangiectatic veins Trombovar and Tromboject are licensed by Health Canada for local injection in sclerotherapy

Table 1: Sclerosing agents [2, 3, 14, 17, 18, 36, 51, 59, 68] (cont'd)

Agent (brand names)	Description and Usage	Complication profile	Regulatory status
Polidocanol (POL) Brand names: Aethxysklerol, Aethoxisclerol, Etoxisclerol, Sotrauerix, Sclerovein Laureth 9	- detergent (emulsifier); mid-potency sclerosing effect; effective at low concentration - commercially available in 0.5% to 5% concentrations - can be used for any dilated vein (higher concentrations of 3% for large veins) - can be diluted for individual cases (1% to 4% for varicose veins) - generally used for medium-sized varicose veins and telagiectasias (0.25% to 0.75%)	Lowest risk for pain and skin necrosis (skin necrosis from painless arteriolar injection) Pigmentation at high concentrations Urticaria (immediate) at injection site Ulceration Rare anaphylaxis	Not FDA approved; currently undergoing review for FDA approval Aethoxysclerol is licenced by Health Canada for esophageal varices and needs special approval from Health Canada for leg vein sclerotherapy [18]
Sodium morrhuate (SM) Brand names: Scleromate	- detergent; biological extract rather than synthetic extract and composition varies from lot to lot; it is unstable in solution - used for varicose veins	Pain Pigmentation Necrosis of skin Highest risk for anaphilaxis	FDA approved for treating vascular ectasias of the lower extremity
Ethanolamine oleate (EO) Brand names: Ethamolin	- detergent; viscous and difficult to inject	Pigmentation Necrosis of skin Pain Pulmonary complications Acute renal failure Hemolytic reactions Risk of urticaria and anaphylaxis	FDA approved for esophageal varices
Polyiodine iodine (PII) Brand names: Variglobin, Sclerodine	- chemical irritant; strong sclerosing effect; it has a dark brown color and it is hard to visualize in the veins - can be diluted for use in reticular and talangiectatic veins	Pain on injection Necrosis of skin Renal insufficiency Anaphylaxis Iodine hypersensitivity reactions	Not FDA approved; Sclerodine licensed by Health Canada for local injection in sclerotherapy
Chromated glycerin Brand names: Chromex, Scleremo	- chemical irritant; weak sclerosing effect; it is viscous and requires dilution prior injection - used for telangiectasias	Pain and cramping Very low risk of pigmentation/ulceration Very rare allergic reaction Ineffective sclerosis	Not approved by FDA for use; not available in North America [17, 18] Available in Europe [18]

FDA – Food and Drug Administration in the United States of America

APPENDIX C: COVERAGE OF SCELROTHERAPY FOR VARICOSE VEINS IN USA

Table 2: Medical coverage policies on sclerotherapy for varicose veins [29-32, 57, 58]

Policy	Covered services	Not covered services
Health Administration Center of the Department of Veterans Affair [58]	USGS is approved for lesser and greater saphenous vein system when there is a justified need for ultrasound as an adjunct to sclerotherapy. Other uses of USGS may be approved for use in cases where sclerotherapy without ultrasound is medically justified.	
Bulletin from AETNA [30]	When medical necessity criteria are met for small to medium sized veins (< 6 mm diameter). After unsuccessful conservative management through a minimum of 6 weeks when saphenous varicosities result in intractable ulceration secondary to venous stasis; or more than 1 episode of minor hemorrhage from a ruptured superficial varicosity; or 1 significant hemorrhage from a ruptured superficial varicosity, especially if transfusion of blood is required.	With or without ultrasound guidance for saphenofemoral junction or saphenous veins. For reflux at saphenofemoral or saphenopopliteal junctions. Ultrasound-monitored or duplex-guided techniques when used solely to guide needle or inject sclerosant in varicose veins.
Medical policy of the Regence Group (independent licensee of the Blue Cross and Blue Shield Association) [31]	Medically necessary for symptomatic varicose veins when a minimum of 6 weeks of non-operative management has failed to adequately relieve symptoms (for the patient to perform daily activities). In addition, the patient has to have symptomatic recurrent or residual varicose veins following ligation and stripping; or symptomatic single veins or small areas of varicose veins, providing essentially all abnormal veins are being treated and there are no remaining significant incompetent veins or perforators.	For very small or reticular veins with questionable symptoms; partial treatment; no documented symptoms; for spider veins or telangectasia. Direct ultrasound visualization of varicose veins during sclerotherapy but the sclerotherapy may be covered if the criteria are met. USGS of greater or lesser saphenous, saphenofemoral junction or perforating veins.
Blue Cross Blue Shield Iowa/South Dakota [57, 32]	If ≥2 of the following are met: symptomatic varicosities which otherwise warrant ligation; intractable pain; 1 phlebitis episode; anatomic derangement beyond simple cosmetic derangement; not treatable varicose veins or failed conservative measures.	Telangiectasia treatment considered cosmetic. Echosclerotherapy treatment of the greater saphenous vein.
New York State Medicare [29]	Compressive sclerotherapy (using empty vein technique followed by compression therapy) is indicated (after failure for conservative management of pain and some complications of varices for 3-6 mo) for local small to medium symptomatic varices, isolated incompetent perforators, or recurrence of symptomatic varices after adequate surgical removal of varices. The following indications when any of them can be attributed to varicosities: pain in affected extremities substantial enough to impair mobility or activities of daily living; significant recurrent superficial phlebitis; skin ulceration; bleeding; or refractory dependent edema or other complications from venous stasis. If performed in conjunction with surgical ligation or stripping procedures.	For large, extensive or truncal varicosities. Microslerosis or injection(s) of sclerosant into spider veins of limbs or trunk is considered cosmetic. When patient is upright and the veins are full (non-compressive sclerotherapy) not considered effective. For varicose veins of legs when services provided by podiatrists.

USGS – ultrasound-guided sclerotherapy or echosclerotherapy

APPENDIX D: RESULTS REPORTED BY PRIMARY RESEARCH

Table 3: Randomized controlled trials on the use of sclerotherapy for varicose veins [59-64]

Study and patient characteristics	Study characteristics	Reported results and adverse effects
Goldman, 2002 [59] ***Age:*** not mentioned ***Gender:*** not mentioned ***Included:*** varicose, reticular, and/or telangiectatic leg veins without incompetence at the SFJ and SPJ junctions ***Excluded:*** not clear	***Sample size:***129 patients ***Protocol:*** each leg was randomly treated with either 0.25%, 0.5%, or 1.5% of STS or 0.5%, 1.0%, or 3% of POL dependent on size category of the veins ***Blinding:*** treating physician blinded to agent injected; evaluators blinded to treatment and study center ***Pre- and post-treatment evaluation:*** photographic assessment; 3 vascular surgeons evaluated photographs for clinical improvement ***Sclerotherapy technique:*** "standard technique as previously described"; concentrations chosen based on clinical and experimental experience ***Success/Failure criteria:*** not clearly stated ***Outcomes:*** overall clinical improvement (disappearance of varicosities measured on a scale of 1-5); patient satisfaction index questionnaire ***Follow-up:*** 1; 4 and 16 weeks	***Results:*** n=42 vein <1mm: moderate disappearance score in both grps (p=0.055) n=41 vein1-3mm: moderate disappearance score both grps (p=0.832) n=46 vein 3-6mm: moderate disappearance score both grps (p=0.581) All veins: moderate disappearance score both grps (p=0.117); average of 70% clinical improvement; 70-72% of patients were satisfied ***Side effects/Complications:*** NSS difference between groups; a decrease in ulceration and swelling in POL group STS: ecchymosis (70%), hyperpigmentation(64%), vein thrombosis(46%), local urticaria (36%), matting (11%), skin necrosis (6.6%), allergic reaction (0%) POL: ecchymosis (58%), hyperpigmentation(53%), vein thrombosis(42%), local urticaria (23%), matting (7%), skin necrosis (0%), allergic reaction (1%)

Table 3: Randomized controlled trials on the use of sclerotherapy for varicose veins [59-64] (cont'd)

Study and patient characteristics	Study characteristics	Reported results and adverse effects
McCoy et al. 1999 [60] ***Age:*** 21 to 76 yrs (av mean 44) ***Gender:*** all women ***Included:*** patients with primary leg idiopathic telangiectasia, with symmetrical areas of vessels on both legs and identifiable reticular feeding veins ***Excluded:*** legs with telangiectasia around ankles or clusters of microvessels secondary to surgical scars; previous sclerotherapy, clinical or Duplex evidence of major saphenous or large perforator incompetence, history of ischemic heart disease, vasculitis, diabetes, pregnancy or regular use of anticoagulants	***Sample size:*** 81 patients ***Protocol:*** morphologically similar telangiectasia and reticular feeding veins identified in matching locations on legs of each patient; one leg randomly assigned to be injected with HS 20%(30% saline/2% lignocain, other leg with 1% POL ***Blinding:*** patients and non-treating physician were blinded to sclerosants ***Pre- and post-treatment evaluation:*** clinical evaluation by treating physician; photographic evaluation by non-treating physician; treatment sites photographed using same camera, lighting conditions, and focal distance, with patient standing ***Sclerotherapy technique:*** supine position; concentrations most commonly used; sufficient solution to blanch a reticular system and all visible branches and telangiectasia; reticular veins injected first; all approached in a "downstream" direction; one treatment per leg; immediate local compression with cotton balls (tape fixation); no graduated compression after treatment ***Success/Failure criteria:*** not clearly stated ***Outcomes (measures):*** pain (0 not painful to 10 extremely painful), patient's satisfaction (scale 0 not satisfied to 10 completely satisfied), treating physician's evaluation (scale 0 no improvement to 10 complete disappearance (estimated percentage of vessel clearance compared to pretreatment photos, and blinded assessment by non treating physician before and after photographs (scale 0 to 10). Adverse effects (telangiectatic matting and hemosiderin staining) scores by treating physician (0 not present to 3 severe) ***Follow-up:*** 2 mo	***Results:*** All legs: mean patient satisfaction score of 7.11 (SD=1.74), mean clinical assessment score of 7.26 (SD=1.47); mean photo rated score of 7.41 (SD=1.5); NSS difference between photo rated score and clinical assessment score (p=0.2) POL: patient satisfaction score of 7.20 (SD=0.19) (SS greater than for HS), mean clinical assessment score of 7.26 (SD=0.21), mean photo rated score of 6.93 (SD=0.20) HS: patient satisfaction score of 7.23 (SD=0.14), means clinical assessment score of 7.56 (SD=0.14), mean photo rated score of 7.3 (SD=0.19) ***Side effects/Complications:*** 5 patients returned before 2 mo due to uncomfortable thromboses (located in 4 HS-treated legs, and 1 POL-treated leg) Pain score for all legs 3.31 (SD=1.60); HS rated SS more painful than POL (p=0.00001) Some evidence of matting n=29 POL treated legs (31%);n=25 HS treated legs (31%) Staining SS more common in POL treated legs (73%) than in HS treated legs (55%) No ulcers and systemic allergy with either HS or POL 1 patient significant swelling and itching in POL treated leg

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Study and patient characteristics	Study characteristics	Reported results and adverse effects
De Roos et al, 2003 [62] (Conducted between September 1996 and October 1998) ***Age:*** older than 18 years ***Gender:*** 80 women; 2 men ***Included:*** legs with lateral accessory varicose veins (LAV) classified as $C_2E_PA_5P_R$ (CEAP classification) ***Excluded:*** deep venous insufficiency, relevant hemodynamic post-thrombotic syndrome, greater saphenous vein incompetence, pregnancy, myocardial decompensation, migraine, hypercoaguable state, other serious illness, dependency edema allergic reaction to Thrombovar (STS), Aethoxysclerol (POL), lidocain, bandage, and arterial disease	***Sample size:*** n=127 eligible legs 106 pts initially randomized; 98 legs in 82 patients (2 treated legs in 16 patients and 1 treated leg in 66 patients), a **computer-generated randomized list** ***Protocol:*** Doppler US exams, digital photoplethysmograpy, SA in n=49 legs or compression sclerotherapy in n= 49 legs ***Blinding:*** no blinding ***Pre- and post-treatment evaluation:*** not clearly described ***Sclerotherapy technique:*** supine position; POL (Aethxysclerol, 3%); aspiration confirmed that needle is located within vein, empty vein technique; immediate local cotton balls compression (tape fixation) for consecutive 4 days and nights; Ccl I stockings after treatment, for 4 consecutive days and nights; Ccl II stockings during day for 10 days ***Stab avulsion:*** Oesch phlebectomy hooks; incisions closed by surgical tape only; bandages applied for 5 days; Ccl II stocking for another 5 days ***Success/Failure criteria:*** not clearly described ***Outcomes (measures):*** observed recurrence and complications ***Follow-up:*** at 2 weeks and 4 weeks (for residual varicose veins), 1 year, and 2 years after sclerotherapy; at 5 days (for removal of bandages) at 2 weeks and 4 weeks (for residual varicose veins), 1 and 2 years after surgery	***Results:*** Recurrence at 1 year: 12 legs sclerotherapy (25%) and 1 leg AP (2.1%); RR for recurrence at 1 year of 12 (95% CI; 1.62 to 88.70) and OR of 15.67 (1.95 to 126.12) Recurrence at 2 years: 18 legs sclerotherapy (37.5%) and 1 leg AP (2.1%); RR of recurrence at 2 years of 18 (95% CI; 2.50 to 129.53) and OR of 28.20 (3.58 to 222.39) Two one-leg-treated patients lost during follow up (1 in AP group and 1 in sclerotherapy group). ***Side effects/Complications:*** blisters occurred during the first 2 weeks only in 15 AP treated legs (31%) (p<0.001) NSS difference in hematoma between treatments (p=1.000) phlebitis in 13 sclerotherapy-treated legs (27%) and in 6 AP treated legs (12%) (p=0.07) scar formation (mostly during 2 weeks post-treatment) only in 8 AP treated legs (17%) (p=0.001) afflictions caused by bandages in 9 AP treated legs (19%), and in 2 sclerotherapy-legs (4%) (p=0.02) telangiectatic matting in 3 AP treated legs (over 2 years) (p=0.039)

Table 3: Randomized controlled trials on the use of sclerotherapy for varicose veins [59-64] (cont'd)

Study and patient characteristics	Study characteristics	Reported results and adverse effects
Lupton et al, 2002 [61] ***Age:*** 27-68 years (mean of 45 years) ***Gender:*** all women ***Included:*** patients with skin phototypes I-III, superficial leg telangiectasia (0.1mm-0.5 mm in diameter; mean 0.5 mm) ***Excluded:*** patients with prior lower extremity telangiectasia treatment, clinical evidence of severe vascular incompetence, on anticoagulant treatment, or those currently pregnant or breastfeeding	***Sample size:*** 20 patients ***Protocol:*** patients randomized to receive 2 treatments with laser irradiation to telangiectases on one leg and with sclerotherapy on the other leg; size matched vessels on thighs, knees, calves, ankles and popliteal fossae were treated by the same operator. All patients received two consecutive treatments at one month intervals. ***Blinding:*** assessors were blinded ***Pre- and post-treatment evaluation:*** not clear whether photographic documentation was obtained before treatment. Post treatment photographic documentation and clinical improvement scores. ***Sclerotherapy technique:*** 0.25% STS (Sotradecol, Elkins-Sinn Inc, Cherry Hill, NJ); sufficient amount injected to blanch vessels and all visible tributaries (range of 2-10ml); graduated compression stockings of 20-30 mmHg applied for 48 hours after treatment ***Laser irradiation technique:*** long-pulsed 1064 nm Nd:YAG laser (Varia, CoolTouch Laser Corp, Auburn, LA), of 25 msec duration for smaller vessels, and of 50 msec for veins >0.5mm in diameter; delivered through a 5 mm collimated spot size at 1Hz; cooling with cryogen spray ***Success/Failure criteria:*** not clearly mentioned/described ***Outcomes (measures):*** photographic documentation and clinical improvement scores on a scale of 0 to 3 by 2 independent assessors at follow-up visits; side effects recorded at each session and follow-up visit ***Follow-up:*** at 1 mo after first session and at 1 and 3 mo after 2nd session	***Results:*** clinical improvement score 26-50% for both sclerotherapy treated legs and for laser treated legs at 1 mo after 1st session at 1 mo after 2nd session, improvement score of 51-75% for sclerotherapy treated legs and 26-50% for laser-treated legs at 3 mo after 2nd session, improvement score of 51-75% for sclerotherapy treated legs and of 26-50% for laser treated legs ***Side effects/Complications:*** both treatments tolerated by all patients, with no serious adverse events n=14/20 (70%) had mild pain associated with both treatments transient local tissue erythema and edema reported by 95% of patients for sclerotherapy treated legs and by 75% of patients for their laser treated legs transient post-inflammatory hyperpigmentation developed in 2 patients (10%) on their sclerotherapy treated legs (both patients had skin phototype III) no cases of vesiculation, fibrosis or scarring after either treatment

Table 3: Randomized controlled trials on the use of sclerotherapy for varicose veins [59-64] (cont'd)

Study and patient characteristics	Study characteristics	Reported results and adverse effects
Belcaro et al, 2003 (VEDICO) [63] Multicentre ***Age:*** 25-65 years ***Gender:*** 33% male ***Included:*** uncomplicated primary varicose veins (no thrombosis, phlebitis, hemorrhage or skin change due to prolonged CVI All patients had incompetence of LSV at SFJ with ≥4 incompetent venous sites. ***Excluded:*** pregnancy, obesity, diabetes, bone/joint problems, post thrombotic occlusion, history of previous thrombosis, coagulation disorders, any cardiovascular or other systemic problems requiring treatment, tumors, bone and joint problems, diabetes, any cause of venous obstruction, severe venous insufficiency , lipodermatosclerosis, ulceration, presence of associated incompetence of SSV	***Sample size:*** 887 patients initially randomized; 749 completed study; intention to treat analysis was used. 'Ideal' sample as 65% of patients were working in hospitals or in a medical environment or were medical staff or relatives of medical personnel, good compliance. Mix of cosmetic, signs, symptoms and fear of complications; AVP,RT, age and sex comparable among grps ***Protocol:*** incompetence evaluated by surgeons with color Duplex scanning performed with patient standing, AVP measurements, venous system and LSV assessed by high resolution probes ; patients randomized to standard sclerotherapy (grp A, n=123); high dose sclerotherapy (grp B n=112); multiple vein ligation (grp C n=132); stab avulsion (grp D n=122); foam sclerotherapy (grp E n=129) surgery (ligation with sclerotherapy) (group F, n=131). A to E treatment within 4 mos; F treatment within 6 mos. Sigvaris stockings (20 to 25 mm at ankle) used during 10 yrs all grps ***Blinding:*** no blinding ***Pre- and post-treatment evaluation:*** color Duplex in association with high-resolution US scanner performed before treatment; AVP recorded before treatment and at 5 and 10 years; Duplex yearly ***Sclerotherapy technique:*** Standard(Grp A):veins>3mm 1-2 ml of 3% STS; veins 2-3mm 2% STS; compression 10-30 days depending on vein diameter High Dose (Grp B): veins>3mm 3-6 ml of 3% STS; compression 1-2 weeks for large veins	***Results:*** 5 year occurrence of new varicose veins varied from 34% in Grp F and Grp C to 44% in Grp E and 48% in Grp A. 10 year occurrence of new varicose veins varied from 37% in Grp F to 56% in Grp A. AVP at 10 years decrease and increase in RT was comparable among all grps. Number of new points of major incompetence was comparable in all treatment groups. ***Side effects/Complications:*** Not reported

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Study and patient characteristics	Study characteristics	Reported results and adverse effects
Belcaro et al, 2003 (VEDICO) [63] (cont'd)	***Surgery:*** Flush ligation (Grp C): closed loop technique, removal of selective ligation of incompetent site Stab avulsion (Grp D): some segments of veins(2-5 cm) removed Foam sclerotherapy (Grp E): US echo; Irving Technique, injection of tensioactive substance under US guidance Surgery and High dose sclerotheapy (Grp F): ligation or stab avulsion plus high dose sclerotherapy. ***Outcomes (measures):*** variations in AVP and refill times (RT) values; presence of duplex reflux; recurrence or new incompetent venous sites ***Follow-up:*** evaluation at 5yrs and 10 yrs	
Belcaro et al. 2000 [64] ***Age:*** 40-60 years ***Gender:*** 51 males and 45 females completed 10-year follow-up ***Included:*** simple superficial venous incompetence (uncomplicated by phlebitis, hemorrhage or ulcerations) ***Excluded:*** previous DVT, episodes of superficial thrombophlebitis, obesity, diabetes, bone/joint problems, hypertension, other	***Sample size:*** 150 patients initially randomized; 29 refused treatment or follow-up or failed to undergo planned treatment; data reported only for those who completed follow-up (96/121 who received treatment) ***Protocol:*** incompetence evaluated with: color Duplex scanning, AVP measurements, strain gauge plethysmograph; no other treatment performed for 10 years; patients randomized to receive ES (group A, n=39), surgery and sclerotherapy (group B, n=40) or surgery only (group C, n=42) ***Blinding:*** no blinding ***Pre- and post-treatment evaluation:*** color Duplex in association with high-resolution US scanner performed before treatment and repeated at every follow up; AVP recorded before treatment and at 5 and 10 years ***Sclerotherapy technique:*** ES: Venocath endovascular catheter (Abott) introduced in LSV under local anesthetic; catheter tip progressed to SFJ and imaged by high resolution US system (ATL Ultramark 9, 7.5 probe) and injected 5-10 ml POL (3%, heated at 45°C);	***Results:*** 25 treated patients (21%) did not complete 10 year follow-up (loss to follow up or failure to comply): 7 grp A, 9 grp B and 9 grp C At 10 years no incompetence observed in subjects treated with SPJ ligation (B and C) In grp A 18.8% of SFJs were patent and incompetent and in 43.8% of limbs the distal venous system was still incompetent as compared to 16.1% in group B ($p < 0.05$) and 36% in group C ($p < 0.05$ vs B and $p=0.05$ vs A). Color duplex of LSV indicated atrophy or obstruction of a segment (mean 6.7 cm) after SFJ ligation (mean 4.2 cm after ES). Mean cost (for evaluation and treatment) of ES was 68% of cost for surgery alone (considered standard cost for this indication) Mean cost of surgery and sclerotherapy was 122% of standard cost

Table 3: Randomized controlled trials on the use of sclerotherapy for varicose veins [59-64] (cont'd)

Study and patient characteristics	Study characteristics	Reported results and adverse effects
Belcaro et al. 2000 [64] (cont'd) significant cardiovascular problems requiring medication, and other clinically significant diseases; previous treatment with surgery and/or sclerotherapy for venous insufficiency of any limb	Femoral vain compressed with pad for 3 min; compression with cotton balls and elastic, adhesive bandage after catheter withdrawal for 3 weeks; graduated compression stockings applied over elastic bandages; patients had to walk for 20 min after procedure and left venous clinic within 30 min Compression sclerotherapy: followed within 3 mo after ES (for residual veins); followed within 3 mo after surgery (for residual veins); no description provided in this paper ***Surgery:*** flush ligation of the incompetent SPJ and collateral veins under spinal or general anesthetic; most important reflux sites detected by color Duplex and marked before surgery; no stripping used ***Outcomes (measures):*** incidence of residual incompetence at 1, 5 and 10 years; cost evaluation ***Follow-up:*** after post-surgical evaluation at 10 days, and at 1, 3 and 6 mo, patients then every 2 years for 10 years	***Side effects/Complications:*** No significant complications were reported; no DVT or superficial vein thrombosis observed following surgery or at 10 years of follow up.

AP – ambulatory phlebectomy; AVP - ambulatory venous pressure; Ccl – compression stockings class I (<25 mm Hg) and class II (25-35 mm Hg); DVI – deep venous insufficiency; DVT - deep venous thrombosis; ES - endovascular sclerotherapy; HS - hypertonic saline; LAV – lateral accessory veins; LSV – long sapenous vein; min – minute(s); mo- month(s); NSS– no (not) statistically significant; POL – polidocanol; RT – refill time; SA – stab avulsion; SD – standard deviation; SFJ – saphenofemoral junction; SPJ – saphenopopliteal junction; SSV – short saphenous vein; STS - sodium tetradecyl sulphate; US – ultrasound/ultrasonography